REMARKS

Amendments in the claims

Following amendment herein, Claims 10–20 are pending in the present application, of which Claims 15–18 are presently withdrawn from consideration. Claims 1–9 were previously canceled and Claim 21 is canceled without prejudice herein.

Claim 19 is amended to further clarify that the claimed compound, when administered to a human body, satisfies the functional test that it is cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin. This amendment is supported by the specification as filed, at least at paragraphs **[0027]**, **[0033]** and **[0034]**.

Claim 21 is canceled as redundant following amendment of Claim 19 herein.

No new matter is added by the present amendment, and no change in inventorship is believed to result therefrom.

RESPONSE TO OFFICE ACTION DATED APRIL 1, 2009

1. Initial comments

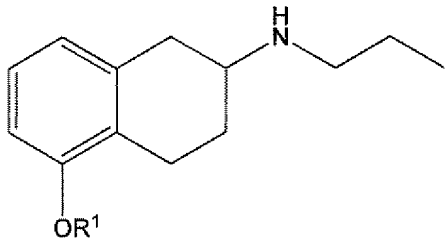
Applicant recognizes that the previous rejections under 35 U.S.C. §112, second paragraph and 35 U.S.C. §102(b) have been withdrawn. In light of the Examiner's statements in conjunction with Applicant's submission below, Applicant believes this application is in condition for allowance.

2. Rejection under 35 U.S.C. §103(a) over Hacksell in view of Wikström and Rodenhuis

Claims 10–12, 14 and 19–21 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hacksell *et al.* (1979) J. Med. Chem. 22(12):1469–1475 ("Hacksell") in view of Wikström *et al.* (1985) J. Med. Chem. 28:215–225 ("Wikström") and Rodenhuis (2000) Dissertation, Rijksuniversiteit Groningen titled "New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation" ("Rodenhuis"). This rejection is respectfully traversed.

2.1. Claim 19

Presently amended Claim 19 is drawn to a compound having the formula



or a salt thereof, wherein the compound is in the (S)-configuration, and wherein when administered to a human body, the compound is cleaved, processed, or metabolized to (S)-2-N-propylamino-5-hydroxytetralin. For at least the reasons set forth below, the present Action fails to make a *prima facie* case of obviousness.

2.1.1. No motivation to select an N-dealkylated compound

After admitting that Hacksell may show a preference for aminotetralins with N,N-dialkylation (Action, p. 4), the Examiner asserts that the disclosure does not teach away from the claimed invention because it does not criticize, discredit or otherwise discourage the solution claimed. The references, however, must be viewed in combination as a whole. See MPEP 2141.02 ("[a]scertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole") (emphasis added). Although the data provided by Hacksell (Table I therein) shows that aminotetralins with N,N-dialkylation are the most active, even if Hacksell provided motivation to select racemic 2-N-propylamino-5-hydroxytetralin (which is not admitted herein, see Section 2.1.2 below), Swart *et al.* (1993) Toxicol. Meth. 3:279–290 ("Swart"), over 10 years after Hacksell, reiterates the state of the art prior to Applicant's invention (emphasis added):

> The N-dealkylated metabolites showed weak affinities in dopaminergic receptor-binding studies, whereas the catechol had an activity comparable to the parent compound. However, because of the high further metabolic conversion in intact organs as well as *in vivo*, it seems unlikely that the catechol metabolite can contribute to the therapeutic efficacy of the parent drug. This possibility is even lower for the N-dealkylated metabolites because of their low receptor affinities.

In other words, both the cited documents and Swart, as a whole, discourage one of skill in the art from selecting a N-dealkylated metabolite of rotigotine. Therefore, Applicant

respectfully submits that one of ordinary skill would have been motivated, if anything, to select an aminotetralin with N,N-dialkylation.

2.1.2. No motivation to select a 2-N-propylamino-5-hydroxytetralin

The cited art also fails to motivate selection of Applicant's specific N-dealkylated compound. The Examiner again cites Hacksell as providing motivation to select racemic 2-N-propylamino-5-hydroxytetralin for further investigation. Specifically, the Action (pp. 3–4) cites Hacksell as allegedly teaching "that racemic 2-N-propylamino-5-hydroxytetralin is a potent dopamine agonist." However, as pointed out in the present specification (paragraph **[0008]**), "the agonistic activity of the substance with an ED_{50} of 40 nM/kg is only moderate and the AUC and the half life are short in comparison to the other evaluated compounds." It is further noted that, of 28 other compounds in Hacksell's Table I for which ED_{50} was determined, at least 8 had a lower limbic ED_{50} than 2-N-propylamino-5-hydroxytetralin; and of 20 other compounds for which AUC was determined, all but one had a higher AUC than 2-N-propylamino-5-hydroxytetralin. Thus Hacksell provides no motivation to specifically select 2-N-propylamino-5-hydroxytetralin.

The Action cites *In re Petering,* 301 F.2d 676 (CCPA 1996) for the proposition that "a generic class encompassing 20 compounds anticipate[s] a claim to one of those compounds" (Action, p. 5). Aside from the point that the present rejection is on grounds of alleged obviousness, not anticipation, the court in *In re Petering* further stated:

> Although it is also true that some of the specific compounds of Karrer ... are structurally rather similar to the compounds defined in [the] claims ... , we have found ... that there is a significant difference in properties between appellants' compounds and Karrer's compounds. ... The former compound is a vitamin, the latter an antivitamin; the former is a metabolite, the latter an antimetabolite; the former acts to promote the well-being of the animal, the later acts to its detriment. ... Karrer leads one away rather than toward compounds with antimetabolic properties. ... We do not agree with the board that the unexpected properties of the compounds defined in [the] claims should not be considered in determining the patentability of these claims.

Instant Claim 19 is drawn to compounds not specifically disclosed in Hacksell (one would have to select Hacksell's compound 8, perform enantioseparation to isolate the (S)-enantiomer, then prepare prodrugs of the (S)-enantiomer to arrive at compounds of Claim 19),

said compounds having different properties from Hacksell's compound 8. Specifically, (S)-2-N-propylamino-5-hydroxytetralin is purely agonistic and has a strongly pronounced functional D3 selectivity. As stated above, the racemate (Hacksell's compound 8) exhibits only moderate agonistic activity. Furthermore, van Vliet *et al.* (1996) J. Med. Chem. 39:4233–4237 concluded that racemic 2-N-propylamino-5-hydroxytetralin did not demonstrate the desired pharmacological profile of a D3-selective antipsychotic. See the specification as filed at paragraph **[0015]**.

Thus (S)-2-N-propylamino-5-hydroxytetralin, not specifically mentioned in Hacksell, exhibits a significant difference in properties from the corresponding racemate. Claim 19 is drawn to prodrugs of (S)-2-N-propylamino-5-hydroxytetralin. No rationale has been articulated, as required for a showing of *prima facie* obviousness under *KSR International Co. v. Teleflex Inc.*, 127 S.Ct.1727, 82 USPQ2d 1385 (2007), why one of ordinary skill would select an indifferent, non-D3-selective compound from Hacksell for enantioseparation followed by prodrug preparation, to provide compounds with markedly different properties. None of the secondary references cited in the present rejection supply the missing motivation.

Rodenhuis is cited as allegedly suggesting formulation of prodrugs; however, absent motivation to select the particular compound (S)-2-N-propylamino-5-hydroxytetralin from which to make prodrugs, this suggestion is not dispositive of obviousness.

Prima facie obviousness of Claim 19 over Hacksell in view of Wikström and Rodenhuis therefore has not been demonstrated.

2.1.3. Rebuttal evidence: unexpected results

Even if *prima facie* obviousness of Claim 19 had been established (which is not admitted herein), the present Action agrees (p. 8) that Applicant's evidence of "unexpected results (*i.e.*, potentially, the pronounced and functional D3 selectivity, pure agonistic activity) may be used to overcome an obvious[ness] type rejection." The Action, however, goes on to state that "the claims must be limited to the unexpected and advantageous results [and that] ... the claims are not limited to these asserted results."

Contrary to this statement, objective evidence of nonobviousness is relevant if it is "commensurate in scope with the claims," and does not require the claims to be "limited to the unexpected and advantageous results" (MPEP 716.02(d)). Because the compounds

embraced by Claim 19 are expressly defined, following amendment herein, to be cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin, the unexpected activity of (S)-2-N-propylamino-5-hydroxytetralin is probative of patentability.

The present specification as filed (see paragraph **[0019]** and Table 1 thereof) shows that (S)-2-N-propylamino-5-hydroxytetralin "in fact binds with a Ki value of 7.6 nM to the D3 receptor"; and "[o]verall the receptor binding tests demonstrate a selectivity D3/D1 and D3/D5 of >1000 and ... D3/D2 of approx. 40 (Table 1)." Furthermore, "the structurally very similar compounds AJ76 and UH232 ... demonstrate[d] a reduced D3 preference" and AJ76 was identified as a pure antagonist, making the D3 selectivity and pure agonist activity of (S)-2-N-propylamino-5-hydroxytetralin even more unexpected. See specification as filed, at paragraph **[0021]**.

2.2. Claim 10

Claim 10 is drawn to a composition containing (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof and at least one pharmaceutically acceptable carrier or adjuvant. Claim 10 is rejected on similar grounds to Claims 19, with the further argument that Hacksell teaches dissolution in saline, occasionally with the addition of a few drops of glacial acetic acid, characterized by the Examiner as a pharmaceutically acceptable carrier or adjuvant, specifically as a buffer.

Claim 10 is drawn to a composition comprising the compound of Claim 19, and is therefore nonobvious for at least the same reasons that Claim 19 is nonobvious. Furthermore, Applicant notes for the record that Hacksell does not disclose, teach or suggest that "[a]ll substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid" (Action, pp. 8–9). Wikström, not Hacksell, tested substance with saline before use, occasionally with the addition of a few drops of glacial acetic acid. However, the compounds tested by Wikström are N,N-dialkylated compounds, which the art clearly distinguishes from N-dealkylated compounds of the present invention. Thus, the cited references fail to disclose, teach or suggest the composition of Claim 10.

2.3. Claims 11, 12, 14 and 20

Claims 11, 12, 14 and 20 depend from independent Claims 10 or 19. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 11, 12, 14 and 20 is nonobvious over the cited references for at least the same reasons that Claims 10 and 19 are nonobvious.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Hacksell in view of Wikström and Rodenhuis is respectfully requested.

3. Rejection under 35 U.S.C. §103(a) over Hacksell in view of Wikström, Rodenhuis and Jansen

Claim 13 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hacksell in view of Wikström and Rodenhuis, and in further view of Jansen *et al.* (1991) Naunyn-Schmiedeberg's Arch. Pharmacol. 343:134–142 ("Jansen"). This rejection is respectfully traversed.

Claim 13 is drawn to a composition of Claim 10 that is adapted for transdermal, transmucosal or parental administration. For reasons set forth above, a *prima facie* case of obviousness of Claim 10 over Hacksell in view of Wikström and Rodenhuis is not sustainable. Jansen is cited for disclosure relevant to transdermal administration as recited in Claim 13, and adds nothing to Hacksell, Wikström and Rodenhuis with respect to obviousness or otherwise of Claim 10; in particular, Jansen fails to provide motivation to specifically select 2-N-propylamino-5-hydroxytetralin for enantioseparation and prodrug derivatization. As Claim 10 is therefore nonobvious over Hacksell in view of Wikström, Rodenhuis and Jansen, the same is true of Claim 13. If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP 2143.03.

Accordingly, notwithstanding any disclosure in Jansen relevant to circumventing "a large gastro-intestinal and hepatic first-pass effect for N-0437…[by] transdermal application of N-0437…and oral administration of ester-prodrugs of N-0437", the Action fails to establish a *prima facie* case of obviousness of Claim 13 over Hacksell in view of Wikström and Rodenhuis and in further view of Jansen.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

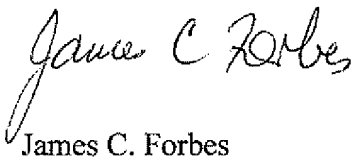
4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner consider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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